American Type Culture Collection

12301 Parklawn Drive • Rockville, MD 20852 USA • Telephone: 301-231-5519 or 231-5532 • FAX: 301-816-4366

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

FAX COPY

COPY

To: (Name and Address of Depositor or Attorney)

LeukoSite, Inc.
Attn: Lijun Wu
215 First Street
Cambridge, MA 02142

Deposited on Behalf of: LeukoSite, Inc. (Ref. Docket No. LKS97-06)

Identification Reference by Depositor:	**ATCC Designation**
Murine hybridoma 2D7 LS100-2D7-13-1-1-14-14-4	HB-12366

The deposit was accompanied by: ___ a scientific description _ a proposed taxonomic description indicated above.

The deposit was received June 6, 1997 by this International Depository Authority and has been accepted.

AT YOUR REQUEST: X We will inform you of requests for the strain for 30 years.

The strain will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strain, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strain.

If the culture should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace it with living culture of the same.

The strain will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the culture cited above was tested June 12, 1997. On that date, the culture was viable.

International Depository Authority: American Type Culture Collection, Rockville, Md. 20852 USA

Signature of person having authority to represent ATCC:

Barbara M. Hailey

Date: June 13, 1997

Barbara M. Hailey, Administrator, Patent Depository

cc: David E. Brook, Esq.

4/15/98

LKS9612.DEC
L/LKS/9612
DEB/HEW/LMT/mrf
12/11/98

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PATENT APPLICATION
Attorney's Docket No.: LKS96-12
Expedited Procedure Under 37 C.F.R. §1.116
Group Art Unit: 1646

#18 (Attach to #17)
BY HAND DELIVERY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Charles R. Mackay and Lijun Wu	
Application No.:	08/739,507	Group: 1646
Filed:	October 28, 1996	Examiner: G. Draper
For:	ANTI-CCR5 ANTIBODIES AND METHODS OF USE THEREFOR	

DECLARATION OF WALTER NEWMAN, PH.D., UNDER 37 C.F.R. §1.132

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Walter Newman, Ph.D., of 3 Durham Street, Apt. 3, Boston, Massachusetts 02115, declare and state that:

1. Since June of 1996, I have been employed as Vice President, Research and Discovery by LeukoSite, Inc., 215 First Street, Cambridge, MA 02142, the assignee of the entire right, title and interest in the above-identified patent application. Prior to my current position, I was employed by LeukoSite, Inc., as Senior Director, Research from 1994 to 1996, and as Director, Research from 1993 to 1994. From 1986 to 1993, I was Chief Scientist of the Endothelial Cell Biology Group at Otsuka America Pharmaceuticals, a biotechnology company. I received both a B.A. in Chemistry and a Ph.D. in Immunochemistry from Columbia University.

EXHIBIT
A

2. I am familiar with the invention claimed in the above-identified application and have studied the application prior to making this Declaration. I have also studied the Office Action, made final, mailed from the U.S. Patent and Trademark Office on April 14, 1998, for the above-identified application.

3. It is very difficult to produce antibodies which are specific to a particular chemokine receptor for several reasons. Seven transmembrane-spanning receptors, including G protein-coupled receptors such as chemokine receptors, are typically not particularly immunogenic in the way that, e.g., soluble receptors, are. One reason for this is that a substantial portion of the receptor is comprised of either the transmembrane or intracellular domains, and is therefore unable to be recognized by an antibody due to that location. Despite the fact that these receptors are relatively large, the portion of the receptor available for recognition by an antibody (i.e., the epitopic regions) is fairly small. Furthermore, chemokine receptors belong to a large superfamily of receptors which share a significant degree of sequence similarity. Thus, the ability of a vacinee's immune system to recognize a particular receptor antigen as foreign and raise an immune response thereto is limited, because the repoirtoire of "self-antigens" is large, thus making it difficult to distinguish the immunogen and self-antigens immunologically. The combination of these factors makes it difficult to produce any antibodies to a chemokine receptor, let alone antibodies which are specific to a particular receptor.

4. CCR5 is a different receptor from CCR3, fusin or the Duffy antigen receptor, and CCR5 is not equivalent to any of these receptors. Each of these receptors has a distinct primary amino acid sequence. CCR5 exhibits a pattern of chemokine binding which is different from that of CCR3, fusin or the Duffy antigen receptor. CCR5 also exhibits a different expression pattern from CCR3, fusin and the Duffy antigen receptor. CCR5 is expressed primarily on T cells and monocytes. In contrast, CCR3 is expressed primarily on eosinophils; the Duffy antigen receptor is expressed primarily on erythrocytes and endothelial cells of post-capillary venules; and fusin is widely expressed. Thus, CCR5 has a different structure and function from CCR3, fusin and the Duffy antigen receptor, and CCR5 is not equivalent to the receptors taught by Feng *et al.*, *Science*, *272*:872-877

(1996); Wasniowska *et al.*, *Molec. Immunol.*, *33*(11/12):917-923 (1996); or Ponath *et al.*, *J. Exp. Med.*, *183*:2437-2448 (1996).

5. Antibodies which bind to CCR5 receptor do not necessarily have the ability to inhibit the binding of a ligand to the receptor. The ability of an antibody to inhibit binding of a ligand to a receptor is dependent upon many factors. For example, one or more structural elements involved in ligand binding must be capable of inducing an immune response. The location of such epitopic regions within a protein is difficult to predict, and there is no reasonable expectation that the ligand binding regions of the receptor protein will be epitopic regions. Furthermore, even if the ligand binding regions are immunogenic, the binding of the resulting antibody to the receptor may not interfere with the binding of a ligand to the receptor. For example, the portion of the receptor which binds to a ligand may have a conformation which allows binding of both the ligand and antibody.

6. Moreover, it is not predictable that the antibodies which are obtained will inhibit one or more functions associated with binding of the ligand to the receptor. Antibodies can function as agonists or antagonists of receptor function. That is, antibodies which bind to a particular receptor and inhibit binding of a ligand to the receptor can inhibit the function associated with the binding of the ligand to the receptor, or can induce or enhance the function associated with binding of the ligand to the receptor. Thus, antibodies which act as agonists of receptor function can "mimic" the effect of ligand binding and cause the same or increased downstream effects as binding of the ligand.

7. During the course of work described in the above-identified application, approximately 18 different hybridoma fusions were screened, two of which produced antibodies reactive with CCR5 transfectants. One of these fusions provided approximately 25 CCR5-reactive supernatants. About one-half of these were subcloned and further characterized. One of these produced antibody 5C7 described in the application. The other fusion produced approximately two reactive supernatants, one of which produced antibody 2D7 described in copending continuation-in-part application U.S. Serial Number 08/893,911, filed July 11, 1997. These data underscore the difficulty in obtaining antibodies to CCR5,

particularly antibodies which inhibit binding of a ligand to CCR5 and inhibit one or more functions associated with binding of a ligand to CCR5.

8. Based on the evidence described in paragraphs (3) through (7) above, there would not have been a reasonable expectation of success in substituting CCR5 for CCR3, fusin or the Duffy antigen receptor to produce antibodies to CCR5 which inhibit the binding of a ligand to the receptor and which inhibit one or more functions associated with binding of the ligand to the receptor. The references cited by the Examiner and the knowledge of the person of ordinary skill in the art did not provide a reasonable expectation of success in producing the claimed invention at the time the application was filed.

9. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Walter Newman, Ph.D.

10/16/98

Date

State of Delaware

Office of the Secretary of State

COPY

I, EDWARD J. FREEL, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF OWNERSHIP, WHICH MERGES:

"LEUKOSITE, INC.", A DELAWARE CORPORATION,

WITH AND INTO "MILLENNIUM PHARMACEUTICALS, INC." UNDER THE NAME OF "MILLENNIUM PHARMACEUTICALS, INC.", A CORPORATION ORGANIZED AND EXISTING UNDER THE LAWS OF THE STATE OF DELAWARE, AS RECEIVED AND FILED IN THIS OFFICE THE SIXTEENTH DAY OF MARCH, A.D. 2000, AT 5:30 O'CLOCK P.M.

Edward J. Freel, Secretary of State

2322355 8100M

001166184

AUTHENTICATION: 0354712

DATE: 03-31-00

3-16-00

CERTIFICATE OF OWNERSHIP AND MERGER

MERGING

LeukoSite, Inc.
(a Delaware corporation)

INTO

Millennium Pharmaceuticals, Inc.
(a Delaware corporation)

Millennium Pharmaceuticals, Inc., a corporation organized and existing under and by virtue of the General Corporation Law of the State of Delaware (the "Corporation"), does hereby certify:

FIRST: That the Corporation was incorporated on the 13th day of January, 1993 pursuant to the General Corporation Law of the State of Delaware.

SECOND: That the Corporation owns all of the outstanding shares of each class of the stock of LeukoSite, Inc., a corporation incorporated on the 1st day of May, 1992 pursuant to the General Corporation Law of the State of Delaware.

THIRD: That the Executive Committee of the Board of Directors of the Corporation, by written consent effective as of the 13th day of March, 2000, duly adopted the following resolutions:

RESOLVED: That, pursuant to Section 253 of the Delaware General Corporation Law, the Corporation is hereby authorized to merge LeukoSite, Inc., a Delaware corporation which is a wholly owned subsidiary of the Corporation, into the Corporation;

RESOLVED: That the President and Secretary of the Corporation be and each hereby is, authorized to execute a Certificate of Ownership and Merger with respect to the merger of LeukoSite, Inc. into the Corporation, cause the same to be filed with the Secretary of State of Delaware and take all such other actions and to execute all such other instruments and agreements as they or any of them may deem appropriate to effect such merger;

RESOLVED: That the merger of LeukoSite, Inc. into the Corporation shall be effective upon the filing of a Certificate of Ownership and Merger with the Secretary of State of Delaware.

IN WITNESS WHEREOF, the Corporation has caused this Certificate to be signed by its authorized officer this 15th day of March, 2000.

MILLENNIUM PHARMACEUTICALS, INC.

By: _____

Title: Secretary
Jack Douglas